PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 01/22753	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US01/90720	International filing date *(day/month/year)* 22 November 2001 (22.11.2001)	Priority date *(day/month/year)* 24 November 2000 (24.11.2000)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/685, 31/215, 31/24, 31/19, 31/20, 31/12, 31/11, 31/075, 31/08; C07F 9/02; C07C 59/235, 43/11 and US Cl.: 514/76, 77, 78, 529, 534, 558, 675, 676, 693, 704, 714, 716, 723; 554/78, 79, 80, 81, 82; 562/578; 560/263, 264, 252; 568/305, 307, 413, 141, 423, 613, 622		
Applicant VASCULAR BIOGENICS LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 June 2002 (11.06.2002)	06 January 2005 (06.01.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Rosalynd Keys Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/90720

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-58 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages NONE, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages 59-65, filed with the letter of 11 September 2003 (11.09.2003)

☒ the drawings:
pages 1-6, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages none

☒ the claims, Nos. 18-22

☒ the drawings, sheets/fig none

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/90720

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	NONE	YES
	Claims	8	NO
Inventive Step (IS)	Claims	1-7, and 9-17	YES
	Claims	8	NO
Industrial Applicability (IA)	Claims	1-17	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claim 8 lacks novelty under PCT Article 33(2) as being anticipated by Boullier et al. (The Journal of Biological Chemistry, 31 March 200, Vol. 275, No. 13, pages 9163-9169). Boullier et al. teach the claimed composition at pages 9163 and 9164 (see also page 9168).

Claims 1-7, and 9-17 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed oxidized phospholipids, compositions comprising said oxidized phospholipids, and the claimed method of making and using said oxidized phospholipids.

Claims 1-17 meet the criteria set out in PCT Article 33(4), because the instant compounds and compositions have pharmaceutical use in the field of cardiology.

---------- NEW CITATIONS ----------

NONE

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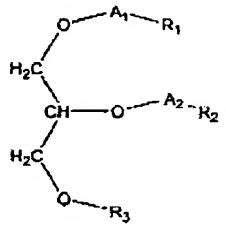
WHAT IS CLAIMED IS:

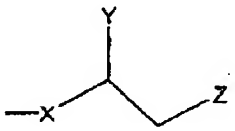
1. A compound having a formula:



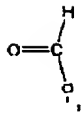
or pharmaceutically acceptable salts thereof, wherein:

(i) A_1 and A_2 are each independently selected from the group consisting of CH_2 and C=O, at least one of A_1 and A_2 being CH_2; and

(ii) R_1 and R_2 are each independently selected from the group consisting of an alkyl chain 1-27 carbons in length and

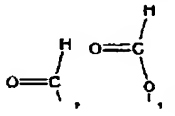


wherein X is a C_{1-24} chain, Y is selected from the group consisting of:



, -OH,–H, alkyl, alkoxy halogen, acetoxy and aromatic functional groups; and

Z is selected from the group consisting of:



, and –OH,

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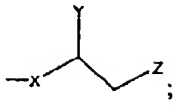
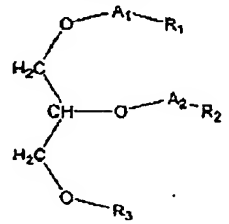
at least one of R_1 and R_2 being said  ; and

(iii) R_3 is selected from the group consisting of H, acyl, alkyl, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl cardiolipin and phosphatidyl inisitol.

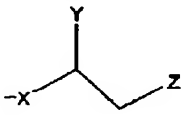
2. A pharmaceutical composition for prevention and/or treatment of atherosclerosis, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, stenosis, restenosis and/or in-stent-stenosis in a subject in need thereof, comprising, as an active ingredient, a therapeutically effective amount of a compound selected from the group having a formula:



or pharmaceutically acceptable salts thereof, wherein:

(i) A_1 and A_2 are independently selected from the group consisting of CH_2 and C=O, at least one of A_1 and A_2 being CH_2; and

(ii) R_1 or R_2 are each independently selected from the group consisting of an alkyl chain 1-27 carbons in length and:



wherein X is C_{1-24}, Y is selected from the group consisting of:

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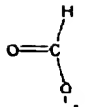
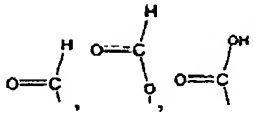
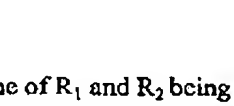

, -OH,-H, alkyl, alkoxy halogen, acetoxy and aromatic functional groups; and

Z is selected from the group consisting of:


and -OH,


at least one of R_1 and R_2 being said ; and

(iii) R_3 is selected from the group consisting of H, acyl, alkyl, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl cardiolipin and phosphatidyl inositol,

and a pharmaceutically acceptable carrier.

3. The composition of claim 2, designed for inducing tolerance to oxidized LDL via mucosal administration.

4. The composition of claim 2, designed for nasal, oral or intra-peritoneal administration.

5. The composition of claim 2, wherein said compound reduces immune reactivity to oxidized LDL in said subject.

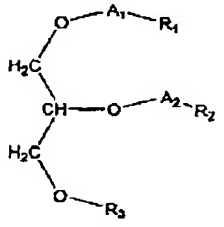
6. The composition of claim 2, packaged and identified for use in the prevention and/or treatment of at least one disorder selected from the group

consisting of atherosclerosis, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, stenosis, restenosis and/or in-stent-stenosis.

7. The composition of claim 2, further comprising a therapeutically effective amount of at least one additional compound selected from the group consisting of HMGCoA reductase inhibitors (statins), mucosal adjuvants, corticosteroids, anti-inflammatory compounds, analgesics, growth factors, toxins, and additional tolerizing antigens.

8. A pharmaceutical composition for prevention and/or treatment of a disease, syndrome or condition selected from the group consisting of atherosclerosis, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, stenosis, restenosis and/or in-stent-stenosis in a subject in need thereof, comprising, as an active ingredient, a therapeutically effective amount of a synthetic oxidized LDL derivative, or pharmaceutically acceptable salts thereof, the composition further comprising a pharmaceutically acceptable carrier.

9. A method of prevention and/or treatment of atherosclerosis, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, stenosis, restenosis and/or in-stent-stenosis in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound, said compound selected from the group having a formula:



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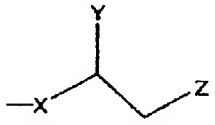
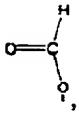
or pharmaceutically acceptable salts thereof, wherein:

(i) A_1 and A_2 are CH_2 or C=O, at least one of A_1 and A_2 being CH_2; and

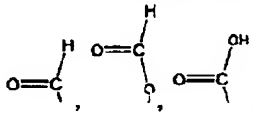
(ii) R_1 or R_2 are each independently selected from the group consisting of an alkyl chain 1-27 carbons in length and:

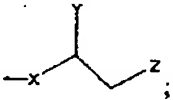


wherein X is C_{1-24}, Y is selected from the group consisting of:

 , -OH,–H, alkyl, alkoxy halogen, acetoxy and aromatic functional groups; and

Z is selected from the group consisting of:

 and -OH,

at least one of R_1 and R_2 being said  ; and

(iii) R_3 is selected from the group consisting of H, acyl, alkyl, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl cardiolipin and phosphatidyl inisitol.

10. The method of claim 9, wherein said compound is administered via mucosal administration.

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11. The method of claim 9, wherein administration of said compound is nasal, oral or intra- peritoneal administration.

12. The method of claim 9, wherein administration of said compound reduces immune reactivity to oxidized LDL in said subject.

13. The method of claim 9, wherein said compound is administered in addition to a therapeutically effective amount of at least one additional compound selected from the group consisting of HMGCoA reductase inhibitors (statins),mucosal adjuvants, corticosteroids, anti-inflammatory compounds, analgesics, growth factors, toxins, and additional tolerizing antigens.

14. A method of synthesizing an oxidized phospholipid comprising:

(a) providing a phospholipid backbone including two fatty acid side chains, wherein at least one of said fatty acid side chains is a mono-unsaturated fatty acid C_{2-15}; and

(b) oxidizing the double bond of said mono-unsaturated fatty acid to thereby generate the oxidized phospholipid.

15. The method of claim 14, wherein said phospholipid backbone further includes a moiety selected from the group consisting of H, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl cardiolipin and phosphatidyl inisitol.

16. The method of claim 14, wherein said mono unsaturated fatty acid is C_{2-15}.

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17. The method of claim 14 wherein the oxidized phospholipid is POVPC, and said mono-unsaturated fatty acid is 5-hexenoic acid.

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